Addition-cyclization reactions of (*Z*)-2,3-diphenylpropenoyl isothiocyanate with aniline and diphenylamine

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Dedicated to Professor P. Hrnčiar, DrSc., in honour of his 60th birthday

The reaction of (*Z*)-2,3-diphenylpropenoyl isothiocyanate with aniline and diphenylamine has been studied. The stable thiourea, formed in the reaction with aniline, in the presence of Lewis acid ($BF_3 \cdot Et_2O$) cyclizes to *cis*-5,6-diphenyl-2-phenylamino-5,6-dihydro-4*H*-1,3-thiazin-4-one. In alkali medium *cis*-1,3-thiazine undergoes Dimroth rearrangement under formation of *cis*-1,5,6-triphenyl-2-thiouracil. *N*-Phenyl-*N'*-(2,3-diphenylpropenoyl)thiourea at similar conditions affords a mixture of *cis*- and *trans*-2-thiouracils. In the reaction with triethylamine both isomers can be isolated. Isomerization of *trans*-2-thiouracil to the *cis* isomer has been studied simultaneously. Diphenylamine with 2,3-diphenylpropenoyl isothiocyanate gives a mixture of *cis*- and *trans*-1,3-thiazines. It was impossible to isolate the corresponding thiourea as *cis*-1,3-thiazine was formed already at low temperature.

Изучена реакция (*Z*)-2,3-дифенилпропеноилизотиоцианата с анилином и дифениламином. Стабильная тиомочевина, образующаяся в реакции с анилином, в присутствии кислоты Льюиса ($BF_3 \cdot Et_2O$) циклизуется в *цис*-5,6-дифенил-2-фениламино-5,6-дигидро-4*H*-1,3-тиазин-4-он. В щелочной среде *цис*-1,3-тиазин подвергается перегруппировке Димрота с образованием *цис*-1,5,6-трифенил-2-тиоурацила. *N*-Фенил-*N'*-(2,3-дифенилпропеноил)тиомочевина в тех же условиях приводит к образованию смеси *цис*- и *транс*-2-тиоурацилов. В реакции с триэтиламином могут быть выделены оба изомера. Одновременно изучалась изомеризация *транс*-2-тиоурацила в *цис*-изомер. Дифениламин реагирует с 2,3-дифенилпропеноилизотиоцианатом с образованием смеси *цис*- и *транс*-1,3-тиазинов. Было невозможно выделить соответствующую тиомочевину, поскольку *цис*-1,3-тиазин образовывался уже при низкой температуре.

Lately, we have focused our attention on the reactions of α,β-unsaturated acyl isothiocyanates with various types of primary and secondary amines. We found that the formed thioureas are suitable intermediates in synthesis of various types of five- and six-membered heterocyclic compounds [1—7], such as benzothiazoles [1, 2], thiazines [3—7], and thiouracils [5—7]. Thioureas,

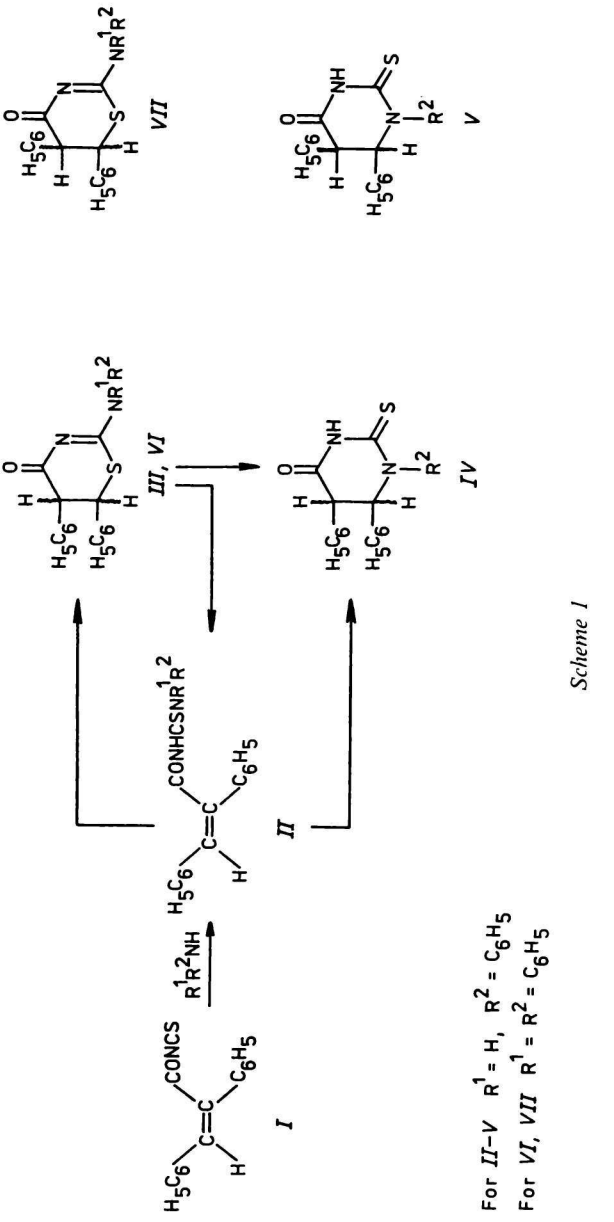
prepared in a similar way from 3-phenylpropenoyl isothiocyanate and 4-substituted anilines, in the presence of sodium ethoxide afforded 2-thiouracils [8]. Of 2-substituted 3-phenylpropenoyl isothiocyanates 2-cyano-3-phenylpropenoyl isothiocyanate was described. This in the reaction with aniline gave thiourea which in alkali medium cyclized to the mixture of *cis*- and *trans*-2--thiouracils [5]. On the other hand, with diphenylamine not thiourea but the mixture of *cis*- and *trans*-1,3-thiazines was obtained directly. So far, there have been two papers in the literature dealing with synthesis of 2,3-diphenylpropenoyl isothiocyanate and its reaction with sodium hydrogensulfide and diazomethane [9, 10].

The aim of the present work was to study the reactions of 2,3-diphenylpropenoyl isothiocyanate with aniline and diphenylamine at various reaction conditions and compare the reactivity with that of 2-cyano-3-phenylpropenoyl isothiocyanate. We followed the effect of the phenyl group against the cyano group on these reactions with regard to the fact that both substituents activate the C=C bond of the 3-phenylpropenoyl residue due to their electron-accepting properties.

From (*Z*)-2,3-diphenylpropenoyl isothiocyanate (*I*) stable thiourea *II* is formed only in the reaction with aniline. This in chloroform in the presence of boron trifluoride is converted by intramolecular cyclization to *cis*-5,6-diphenyl--2-phenylamino-5,6-dihydro-4*H*-1,3-thiazin-4-one (*III*, Scheme 1). It was found that the configuration of the obtained *cis* isomer is not dependent on concentration of boron fluoride. By increasing the mole ratio of boron fluoride the reaction time shortens. When 7.5 mmol of boron fluoride is used per 5 mmol of thiourea *II* the reaction time is 4 d, with 10 mmol it is 1 d, and with 20 mmol it is 95 min.

It is known from the literature that various types of 5- and 6-membered heterocyclic compounds containing in the ring nitrogen, oxygen, and sulfur readily undergo Dimroth rearrangement [11—14] either on heating or under catalytic action of acids or alkalis. On the basis of the mentioned fact we obtained *cis*-1,5,6-triphenyl-2-thiouracil (*IV*) from *III* by using lithium hydride in dimethylformamide and sodium hydroxide or triethylamine in anhydrous ethanol. Rearrangement with lithium hydride or sodium hydroxide proceeds at room temperature, with triethylamine on heating. At room temperature the Dimroth rearrangement does not take place, but after 52 h thiourea *II* is obtained.

Further, we carried out cyclization of *II* in alkali medium (ethanolic or aqueous solution of sodium hydroxide). In these reactions a mixture of both isomers of 2-thiouracil *IV*, *V* was formed. Preparation of pure *cis* and *trans* isomers from thiourea is possible in the presence of triethylamine and is dependent on concentration. When the ratio is 5 mmol of triethylamine per 4 mmol


VII
V
III, VI
IV
II
I
CONCS
R1R2NH
CONHCSNR1R2
For II–V R1 = H, R2 = C6H5
For VI, VII R1 = R2 = C6H5

Scheme 1

of thiourea, the pure *trans* isomer *V* is isolated from the reaction mixture. When 10 mmol of triethylamine is used a mixture of both isomers is formed which can be separated on a silica gel column. From this dependence we deduced that the increase of the mole ratio of triethylamine must lead to subsequent isomerization of *trans* isomer to *cis* isomer. To confirm this assumption, 25-fold amount of triethylamine (100 mmol) was added to the *trans* isomer. After 35 h reflux in ethanol we obtained the pure *cis* isomer *IV*. This can be prepared in high yield (90 %) also by the reaction of thiourea *II* with lithium hydride in dimethylformamide.

In the reaction of diphenylamine with isothiocyanate *I* (Scheme 1) 1,3-thiazines *VI* and *VII* were formed directly, without the possibility to isolate thiourea. At 10 °C in benzene the *cis* isomer *VI* was formed, while under reflux the mixture of both isomers which could not be separated either chromatographically or by crystallization.

The obtained results suggest that 2,3-diphenylpropenoyl isothiocyanate in the reaction with aniline and diphenylamine affords analogous products as 2-cyano-3-phenylpropenoyl isothiocyanate.

2-Thiouracils may be distinguished from 1,3-thiazines by means of IR spectroscopy on the basis of stretching vibrations of their carbonyl groups. The absorption band belonging to carbonyl group of 2-thiouracils (*IV*, *V*) with the —NH—CO— atomic grouping was shifted significantly to higher wavenumbers (ν(CO) 1717, 1710) against that of 1,3-thiazines (*III*, *VI*) (ν(CO) 1667, 1653) where the C=N—C=O conjugation operates. To prove the *cis-trans* isomerism we made use of the ^{1}H NMR spectra where the vicinal coupling constants $^3J_{AB}$ make possible to ascribe both configurations. It is known from the literature [15] that *trans* isomers of cyclic compounds have higher coupling constants than *cis* isomers. From the values measured it follows that the derivatives *III*, *IV*, and *VI* with lower coupling constants ($^3J_{AB}$ = 1.6—4.2 Hz) are *cis* isomers and the compounds *V* and *VII* with higher coupling constants ($^3J_{AB}$ = 6.0—9.8 Hz) are *trans* isomers. *Giordanno* [16] gives for the similar type of *cis*-1,3-thiazine the coupling constant $^3J_{AB}$ = 3.3 Hz and for the *trans* isomer $^3J_{AB}$ = 8.4 Hz. The ratio of geometric isomers in the synthesized mixture of 1,3-thiazines *VI*, *VII* was determined from the integrated intensities of the —CH—CH— doublets in the ^{1}H NMR spectra. The *cis* isomer *VI* amounted to 44 % and the *trans* isomer *VII* to 56 %.

Experimental

(*Z*)-2,3-Diphenylpropenoyl isothiocyanate (*I*) was prepared according to [9]. Infrared spectra were measured in chloroform with an IR 75 (Zeiss, Jena) spectrophotometer. The $\tilde{\nu}$ values are given in cm^{-1}. ^{1}H and ^{13}C NMR spectra were measured in

deuterochloroform with a Tesla BS 487 A (80 MHz) and a Tesla 567 (25.15 MHz) spectrometers, respectively, using tetramethylsilane as internal standard. The values of chemical shifts δ are given in ppm. The coupling constants of the synthesized mixtures of *cis*- and *trans*-1,3-thiazines *VI*, *VII* and 2-thiouracils *IV*, *V* were measured by the INDOR technique in the CW regime. The reaction course was monitored by thin-layer chromatography on Silufol plates (Kavalier, Votice).

N-Phenyl-N'-(2,3-diphenylpropenoyl)thiourea (II)

Method A

Isothiocyanate *I* (15 mmol) was dissolved in cyclohexane (50 cm^3) under vigorous stirring and aniline (15 mmol) was added. In the course of the reaction a precipitate was formed. The mixture was stirred for 30 min at room temperature. The solid product was sucked, washed with cyclohexane, dried, and crystallized from ethanol. Yield = 74 %, m.p. = 130.5—131.5 °C. For $C_{22}H_{18}N_2OS$ (M_r = 358.5) w_i(calc.): 73.71 % C, 5.06 % H, 7.82 % N; w_i(found): 73.65 % C, 5.20 % H, 7.68 % N. IR spectrum: 1495 ν(NHCS), 1585 ν(C=C), 1670 ν(C=O), 3385 ν(NH). ^{1}H NMR spectrum: 7.30 (m, C_6H_5), 7.93 (s, CH=), 8.32 (s, NH). ^{13}C NMR spectrum: 141.84 and 128.41 (d, s, CH=C), 137.74, 133.86, 133.56, 132.44, 130.87, 130.35, 129.97, 129.75, 128.78, 126.69, 123.85 (s, s, s, d, d, d, d, d, d, d, d, C_6H_5), 166.78 (s, C=O), 177.98 (s, C=S).

Method B

Thiazine *III* (2 mmol) was dissolved in the mixture of ethanol (20 cm^3) and chloroform (20 cm^3). Then triethylamine (4 mmol) was added and the mixture was allowed to stand at room temperature for 52 h. After evaporation of solvents the solid residue was crystallized from ethanol. Thiourea *II* was obtained in 74 % yield.

cis-5,6-Diphenyl-2-phenylamino-5,6-dihydro-4H-1,3-thiazin-4-one (III)

Thiourea *II* (5 mmol) was dissolved in chloroform (10 cm^3) with stirring and $BF_3 \cdot Et_2O$ (10 mmol) was added dropwise. The mixture was allowed to stand at room temperature for 1 day. After termination of the reaction, the mixture was diluted with chloroform (30 cm^3) and neutralized with 4 % sodium hydrogencarbonate (31.2 cm^3). The chloroform layer was separated, dried with anhydrous magnesium sulfate and after evaporation of chloroform the solid residue was crystallized from ethanol. Yield = 57 %, m.p. = 147—148 °C. For $C_{22}H_{18}N_2OS$ (M_r = 358.5) w_i(calc.): 73.71 % C, 5.06 % H, 7.82 % N; w_i(found): 73.62 % C, 5.15 % H, 7.73 % N. IR spectrum: 1590 ν(N=C—S), 1667 ν(C=O), 3433 ν(NH). ^{1}H NMR spectrum: 4.26 and 4.90 (d, d, CH—CH, $^3J_{AB}$ = 4.07 Hz), 7.00 (m, C_6H_5). ^{13}C NMR spectrum: 46.73 and 54.79 (d, d, CH—CH), 136.39, 134.38, 130.35, 129.75, 129.45, 128.56, 128.11, 124.30, 121.46 (s, s, s, d, d, d, d, d, d, C_6H_5), 151.10 (s, C=N), 171.26 (s, C=O).

cis-1,5,6-Triphenyl-2-thiouracil (IV)

Method A

Thiourea *II* (4 mmol) was dissolved in anhydrous ethanol (60 cm^3) at heating and triethylamine (10 mmol) was added. The mixture was refluxed for 1 h. After cooling the solid residue was sucked and purified on a silica gel column using chloroform—petroleum ether ($\varphi_r = 7 : 1$) as the eluent. The *cis* isomer *IV* was obtained after crystallization from ethanol in 60 % yield. M.p. = 235—236.5 °C. For $C_{22}H_{18}N_2OS$ ($M_r = 358.5$) w_i(calc.): 73.71 % C, 5.06 % H, 7.82 % N; w_i(found): 73.79 % C, 5.10 % H, 7.62 % N. IR spectrum: 1475 ν(NHCS), 1710 ν(C=O), 3378 ν(NH). ^{1}H NMR spectrum: 4.11 and 5.05 (d, d, CH—CH, $^3J_{AB} = 1.6$ Hz), 7.10 (m, C_6H_5). ^{13}C NMR spectrum: 53.58 and 69.70 (d, d, CH—CH), 144.08, 137.29, 136.10, 129.45, 129.30, 128.78, 128.56, 128.18, 127.21, 126.91, 126.09 (d, s, s, d, d, d, s, d, d, d, d, C_6H_5), 165.93 (s, C=O), 179.22 (s, C=S).

The *trans* isomer *V* was obtained in 18 % yield.

Method B

Thiourea *II* and thiazine *III*, respectively (5 mmol) was dissolved in dimethylformamide (10 cm^3) and lithium hydride (7.5 mmol) was added. The mixture was stirred at room temperature for 3 h. After termination of the reaction water (80 cm^3) was added and the mixture was neutralized with diluted hydrochloric acid. The obtained solid product *IV* was sucked, dried, and crystallized from ethanol. Yield = 90 % and 68 %, respectively.

Method C

Thiazine *III* (5 mmol) was dissolved in minimum amount of ethanol and 2 M-NaOH (5 mmol) was added. The mixture was allowed to stand at room temperature for 4 d, then it was diluted with water (100 cm^3) and neutralized with 2 M-HCl. The formed precipitate was sucked and crystallized from ethanol. Yield = 42 %.

Method D

Thiazine *III* (5 mmol) was dissolved in anhydrous ethanol (80 cm^3) and triethylamine (6 mmol) was added. The mixture was refluxed for 1 h and cooled. The solid product was sucked, dried, and crystallized from ethanol. Yield = 51 %.

Method E

trans-2-Thiouracil *V* (2.8 mmol) was dissolved in anhydrous ethanol (60 cm^3) and triethylamine (70 mmol) was added dropwise. The mixture was refluxed for 35 h and cooled. The solid product was sucked, dried, and crystallized from ethanol. Yield = 61 %.

trans-1,5,6-Triphenyl-2-thiouracil (V)

Thiourea *II* (4 mmol) was dissolved at heating in anhydrous ethanol (60 cm^3) and triethylamine (5 mmol) was added. The mixture was refluxed for 1 h and cooled. The solid product was sucked and crystallized from ethanol. Yield = 63 %, m.p. = = 247—249 °C. For $C_{22}H_{18}N_2OS$ (M_r = 358.5) w_i(calc.): 73.71 % C, 5.06 % H, 7.82 % N; w_i(found): 73.53 % C, 5.18 % H, 7.61 % N. IR spectrum: 1467 ν(NHCS), 1718 ν(C=O), 3382 ν(NH). ^{1}H NMR spectrum: 4.80 and 4.96 (d, d, CH—CH, $^3J_{AB}$ = 6.00 Hz), 7.00 (m, C_6H_5), 11.14 (s, NH). ^{13}C NMR spectrum: 50.76 and 69.26 (d, d, CH—CH), 143.99, 135.10, 132.56, 130.47, 128.68, 128.16, 127.49 (s, s, s, d, d, d, d, C_6H_5), 166.16 (s, C=O), 178.85 (s, C=S).

cis-2-Diphenylamino-5,6-diphenyl-5,6-dihydro-4H-1,3-thiazin-4-one (VI)

Isothiocyanate *I* (12 mmol) was dissolved in anhydrous benzene (10 cm^3) and the solution was cooled to 10 °C. Then diphenylamine (12 mmol) in anhydrous benzene (4 cm^3) was added dropwise under vigorous stirring. Within 30 min a solid precipitated. This was sucked, washed with hexane, dried, and crystallized from ethanol. Yield = 49 %, m.p. = 195 °C. For $C_{28}H_{22}N_2OS$ (M_r = 434.6) w_i(calc.): 77.39 % C, 5.10 % H, 6.45 % N; w_i(found): 77.31 % C, 5.21 % H, 6.36 % N. IR spectrum: 1471 ν(N=C—S), 1653 ν(C=O). ^{1}H NMR spectrum: 4.14 and 4.87 (d, d, CH—CH, $^3J_{AB}$ = 4.20 Hz), 7.11 (m, C_6H_5).

Mixture of cis- and trans-2-diphenylamino-5,6-diphenyl-5,6-dihydro-4H-1,3-thiazin-4-one (VI, VII)

To the solution of isothiocyanate *I* (12 mmol) in anhydrous benzene (25 cm^3) diphenylamine (12 mmol) dissolved in benzene (10 cm^3) was added. The mixture was refluxed for 90 min, then cooled in ice water bath. The formed product was sucked, washed with benzene, dried, and crystallized from the mixture of chloroform—petroleum ether. Yield = 66 %, m.p. = 171—172 °C. For $C_{28}H_{22}N_2OS$ (M_r = 434.6) w_i(calc.): 77.39 % C, 5.10 % H, 6.45 % N; w_i(found): 77.40 % C, 5.18 % H, 6.30 % N. IR spectrum: 1467 ν(N=CS), 1650 ν(C=O). ^{1}H NMR spectrum: 4.14 and 4.87 (d, d, CH—CH, $^3J_{AB}$ = 4.20 Hz) for the *cis* isomer *VI* and 4.10 and 4.78 (d, d, CH—CH, $^3J_{AB}$ = 9.80 Hz) for the *trans* isomer *VII*, 7.11 (m, C_6H_5).

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